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Clinical Investigation

Temporal Cerebral Microbleeds Are Associated With Radiation Necrosis and Cognitive Dysfunction in Patients Treated for Nasopharyngeal Carcinoma

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Summary

This study revealed the severity of cerebral microbleeds (CMBs) in radiation-induced brain necrosis (RN) and the cognitive impact of CMBs in patients with RN. We found that in patients undergoing radiation therapy, CMBs presented most commonly in temporal lobes. The number of temporal lobe

Purpose: Radiation therapy for patients with nasopharyngeal carcinoma (NPC) may be complicated with radiation-induced brain necrosis (RN), resulting in deteriorated cognitive function. However, the underlying mechanism of this phenomenon remains unclear. This study attempts to elucidate the association between cerebral microbleeds (CMBs) and radiation necrosis and cognitive dysfunction in NPC patients treated with radiation therapy.

Methods and Materials: This cross-sectional study included 106 NPC patients who were exposed to radiation therapy (78 patients with RN and 28 without RN). Sixty-six patients without discernable intracranial pathology were included as the control group. CMBs were confirmed using susceptibility-weighted magnetic resonance imaging. Cognitive function was accessed using Montreal Cognitive Assessment. Patients with a total score below 26 were defined as cognitively dysfunction.

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CMBs was significantly associated with volume of brain necrosis and cognitive dysfunction.

Results: Seventy-seven patients (98.7%) in the RN group and 12 patients (42.9%) in the non-RN group had at least 1 CMB. In contrast, only 14 patients (21.2%) in the control group had CMBs. In patients with a history of radiation therapy, CMBs most commonly presented in temporal lobes (76.4%) followed by cerebellum (23.7%). Patients with RN had more temporal CMBs than those in the non-RN group (37.7 ± 51.9 vs 3.8 ± 12.6, respectively; $P<.001$). The number of temporal lobe CMBs was predictive for larger volume of brain necrosis ($P<.001$) in multivariate linear regression analysis. Although cognitive impairment was diagnosed in 55.1% of RN patients, only 7.1% of non-RN patients sustained cognitive impairment ($P<.001$). After adjusting for age, sex, education, period after radiation therapy, CMBs in other lobes, and RN volume, the number of temporal CMBs remained an independent risk factor for cognitive dysfunction (odds ratio [OR]: 1.03; 95% confidence interval [CI]: 1.01-1.04; $P=.003$).

Conclusions: CMBs is a common radiological manifestation in NPC patients with RN. The number of temporal CMBs is independently associated with increased likelihood of cognitive dysfunction in patients with RN.

Introduction

Nasopharyngeal carcinoma (NPC) is a prevalent disease in southern China (1), especially in Guangdong province. Radiation therapy is the standard radical treatment for NPC but may cause transient as well as long-term complications (2). Radiation-induced brain necrosis (RN) is one of the severe complications that potentially leads to cognitive dysfunction, seizure, headache, and limb paralysis. The incidence rate of RN has been demonstrated to directly correlate with the modality of radiation therapy and was suggested in previous studies to have lower occurrences in patients treated with intensity modulated radiation therapy (IMRT) (3, 4). According to our previous study results, NPC patients with RN may present significant cognitive impairment compared with those without RN (5). In contrast to other complications that have more compelling presentations and therefore are largely reported in studies, cognitive impairment has a subtle pathophysiological presentation that has not been adequately appreciated but has a marked impact on the irradiated patient's subsequent quality of life (5-7). However, despite clear indications of association between RN and cognitive impairment, the underlying mechanism has yet to be established.

Cerebral microbleeds (CMBs), defined as hemorrhagic microvascular lesions or microangiopathy in the brain, are well known to progressively affect the function of the neurovascular unit and result in cognitive dysfunction (8-10). Werring et al (11) retrospectively analyzed 55 patients with suspected stroke or transient ischemic attacks and revealed independent association between CMBs and cognitive dysfunction, regardless of the extent of white matter changes of presumed ischemic origin or the presence of ischemic stroke. From our clinical experience, CMBs are frequently detected in patients with RN. Based on these observations, we hypothesized that CMBs might be associated with cognitive impairment in RN patients. We initiated a cross-sectional study to evaluate the prevalence and severity of CMBs in NPC patients after radiation therapy by susceptibility-weighted magnetic resonance imaging (SWI). Results were compared with those for 66 individuals without a history of radiation therapy or traumatic brain injury (control group). We also explored the relationship among CMBs, volume of brain necrosis, and cognitive function in patients with RN.

Methods and Materials

Patient population

We prospectively included patients who underwent radiation therapy at least 12 months prior to admission within the neurology department of our hospital between February 2012 and January 2014. Patient baseline information was retrospectively collected from chart reviews. Patients with the following criteria were excluded from the study: those with (*1*) a present diagnosis of intracranial cancer metastases; or a history of (*2*) cerebrovascular disease or Alzheimer disease; (*3*) hypertension and diabetes; (*4*) other neurological diseases accompanied by cognitive dysfunction; and (*5*) severe dementia or an altered level of consciousness. In the same period, inpatients within the same department without radiation therapy who did not match any exclusion criteria were recruited as controls.

The diagnosis of RN was defined as a lesion of high intensity on T2-weighted images and a lesion of enhancement on post-contrast images, particularly with "soap bubble" or "Swiss cheese" enhancement (12, 13). Cognitive function was evaluated by Montreal Cognitive Assessment (MoCA) scale (Chinese version); CMB-related information was assessed by SWI; and the volume of RN was measured

by T2-weighted FLAIR imaging. Patient characteristics including age, sex, educational background, radiation dose, radiation technique, and post-radiation therapy follow-up interval were also collected. This study was approved by the institutional ethics review board of our hospital. Informed consent was obtained from all enrolled patients.

Brain imaging

Magnetic resonance imaging (MRI) was performed using a 1.5-T whole-body MRI system (Gyroscan Intera; Philips, Aachen, Germany), with an 8-channel phased-array head coil. Imaging protocol included the following pulse sequences: (*1*) axial T2-weighted imaging (20 slices; field of view = 250 mm; slice thickness = 5 mm; gap = 1.0 mm, repetition time [TR] = 4400 ms; TE = 110 ms; flip angle = 90°); (*2*) axial SWI (100 slices; field of view = 250 mm; voxel size = 1 × 1 × 1.2 mm; TE = 40 ms; TR = 35 ms; flip angle = 15°). SWI images were constructed by multiplying magnitude images with filtered phase images to enhance the susceptibility effect, and then a minimum-intensity projection reconstruction was performed with a slice thickness of 6 mm and an interslice gap of 1 mm. (*3*) Axial T1-weighted imaging (20 slices; field of view = 250 mm; slice thickness = 5 mm; gap = 1.0 mm; TR = 540 ms; TE = 15 ms; flip angle = 70°); (*4*) coronal T2-weighted FLAIR imaging (18 slices; slice thickness = 5 mm; gap = 1.5 mm; TE = 180 ms; TR = 11,000 ms; TI = 2800 ms); and (*5*) axial T1-weighted enhancement scans (Gd-EDPA; 0.2 mL/kg [Magnevist, Bayer Schering Pharma AG, Berlin, Germany]) use the same scan parameters as for T1-weighted imaging. CMBs were defined as hypointense homogeneous foci of at least 10 mm in diameter demonstrated on SWI sequences; symmetrical hypointensities in the globus pallidus and flow voids from cortical vessels were disregarded. Images were interpreted by a neuroradiologist who was blinded to the clinical diagnosis.

Cognitive function evaluation

Patient cognitive function at follow-up was assessed by using the MoCA scale (Chinese version), which consists of 7 different cognitive domains: visuospatial and executive abilities, naming, attention, language, abstraction, delayed recall memory, and orientation (14). Each domain has a maximum score range from 2 to 6, and the final score of MoCA was defined as the total score of all 7 domains. A total score less than 26 was determined to indicate cognitive dysfunction in our study.

Statistical analysis

Continuous variables were described as means and standard deviations, whereas categorical variables were presented in numbers and percentages. Analysis of variance (ANOVA) and post hoc tests were used to detect differences in age, post-radiation therapy interval, radiation dose, and number of microbleeds between groups, whereas Wilcoxon and χ^2 tests were used for comparison of educational background and sex, respectively. Cognitive function was divided into 2 categories, normal cognitive function (MoCA $\geq$ 26) and cognitive dysfunction (MoCA $<$ 26). All variables were included in multiple linear regression and multivariate logistic regression models to adjust for confounding factors. All *P* values were reported as 2-sided with significance level defined as a *P* value of $<$.05. All statistical analysis was performed using Stata version 13.0 software (Stata Statistical Software, College Station, TX).

Results

Patient population and baseline demographics

After we applied inclusion and exclusion criteria, a total of 172 patients were identified and included in our study. In 172 patients, 106 patients (61.6%) underwent radiation therapy and were further divided into the RN group (n = 78) and the non-RN group (n = 28). Another 66 patients were included as the control group to fully appreciate the effect of radiation therapy on the number of CMBs, and their diagnoses were as follows: n = 18 cervical spondylosis, n = 13, facial nerve palsy, n = 11 polymyositis, n = 10 myasthenia gravis, n = 9 mild depression, and n = 5 Guillain-Barre syndrome. A detailed flow-chart of participant selection is shown in Figure 1.

As shown in Table 1, age at diagnosis and education background were similar across comparison groups. No significant differences were found in terms of proportion of IMRT, radiation dose, period of time since radiation therapy, and the proportion of those receiving chemotherapy in the RN group compared to that in the non-RN group. However, more male patients than controls were treated with radiation therapy (*P* = .002), with the RN group having the highest proportion of male patients (n = 57; 73.1%).

Cerebral microbleeds

At least 1 CMB was found in 77 patients (98.7%) in the RN group, in 12 patients (42.9%) in the non-RN group, and in 14 patients (21.2%) in the control group. For patients who previously underwent radiation therapy, CMBs occurred most frequently (76.4%) in temporal lobes (Fig. 2), followed by cerebellum (23.7%), basal ganglia (15.8%), occipital lobe (10.5%), brain stem (9.2%), and frontal lobe (3.9%). To clarify whether radiation therapy was associated with a higher propensity for CMBs, we compared the number of CMBs in patients with a history of radiation therapy with that of patients without a history of radiation therapy. Results showed that patients with radiation therapy presented with more CMBs (29.8 ± 48.0 vs 0.7 ± 2.1, respectively; *P*$<$.001) than their counterparts. To account

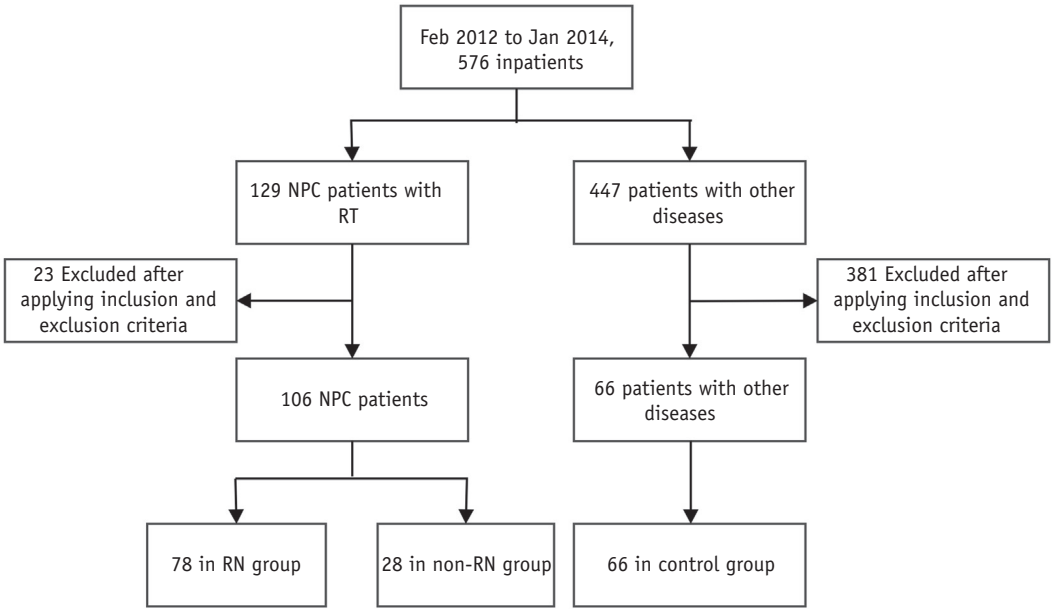

Fig. 1. Flow chart of study cohort selection. *Abbreviations:* NPC = nasopharyngeal cancer; RN = radiation-induced brain necrosis.

for sex differences between radiation therapy and non-radiation therapy groups, we further stratified our data by sex and found that the association between radiation therapy and CMBs was still significant in each sex stratum (males, $P<.001$; females, $P=.003$). We also compared the differences between numbers of CMBs in the control group with those in the non-RN group but failed to observe a difference in the number of CMBs in each individual patient between those 2 groups (0.7 ± 2.1 vs 4.2 ± 12.7, respectively; $P=.156$), which suggested that RN was a stronger indicator of CMBs than radiation therapy, as we have shown that the development of CMBs is associated with RN but not necessarily with radiation therapy. In addition, we observed significant differences between numbers of CMBs in temporal lobes in RN patients compared to those in non-RN patients (37.7 ± 51.9 vs 3.8 ± 12.6, respectively $P<.001$). Conversely, the number of CMBs was not associated with RN in other locations of the brain ($P=.169$). Multivariate linear regression demonstrated that higher numbers of temporal lobe CMBs was an independent indicator (correlation coefficient = 0.45; 95% confidence interval [CI]: 0.26-0.64; $P<.001$) of larger volume of brain necrosis (Table 2) after adjusting for other baseline demographic variables.

Cognitive function

Within our study cohort, a total of 43 RN patients (55.1%) and 2 non-RN patients (7.1%) were determined to be cognitively impaired according to our study definition, and all subjects in the control group were cognitively functional. Patients in the RN group demonstrated lower MoCA scores than non-RN and control groups (24.8 ± 3.7 vs

Table 1 Comparison between patient baseline characteristics in different groups

Parameter	Control group (N=66)	Non-RN group (n=28)	RN group (n=78)	*P* value
Age (±SD) (y)	48.8 (15.2)	47.9 (7.2)	46.8 (8.6)	.574
Sex				
Males (%)	30 (45.5)	19 (67.9)	57 (73.1)	.002*
females (%)	36 (54.5)	9 (32.1)	21 (26.9)	
Education				
Primary school (%)	4 (6.1)	1 (3.6)	10 (12.8)	.323
High school (%)	34 (51.5)	15 (53.6)	41 (52.6)	
College or above (%)	28 (42.4)	12 (42.9)	27 (34.6)	
Post-RT interval (±SD) (y)	-	5.3 (3.5)	6.5 (3.9)	.167
Radiation dose (Gy)	-	70 (70-72)	71 (66-76)	.428
IMRT (%)	-	9 (32.1)	29 (37.2)	.819
Chemotherapy (%)	-	21 (75.0)	61 (78.2)	.728

Abbreviations: CMBs = cerebral microbleeds; IMRT = intensity modulated radiation therapy; RN = radiation-induced brain necrosis; RT = radiation therapy; SD = standard deviation.

* Significant variables ($P<.050$).

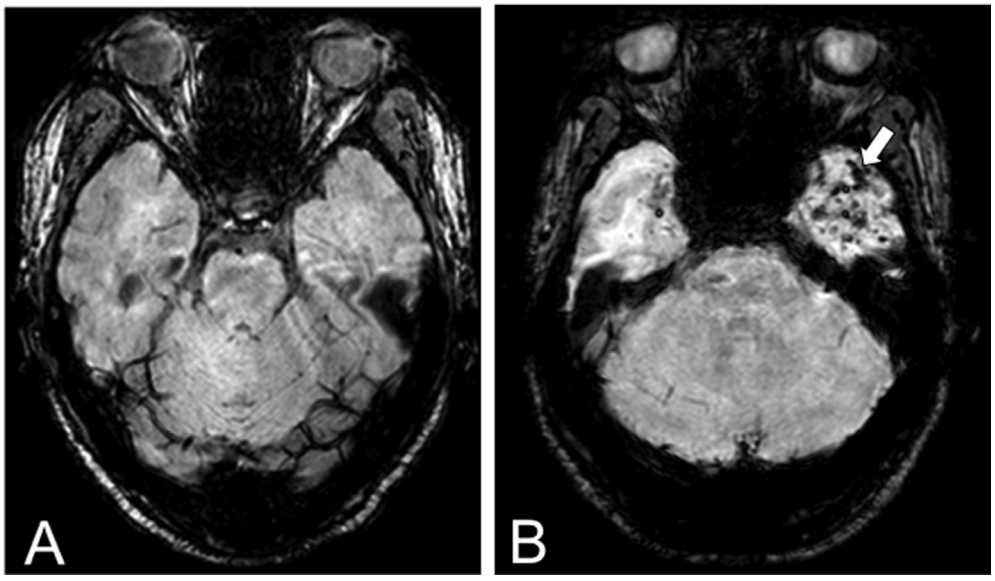

Fig. 2. SWI of (A) a 55-year-old male patient without brain necrosis (RN) after radiation therapy. (B) A 50-year-old male patient with brain necrosis. Arrow indicates cerebral microbleeds. *Abbreviations:* RN = radiation-induced brain necrosis; SWI = susceptibility-weighted magnetic resonance imaging.

28.1 ± 2.0, respectively; $P<.001$; 24.8 ± 3.7 vs 29.1 ± 0.8, respectively; $P<.001$). Interestingly, despite a lack of radiological evidence of brain necrosis, patients in the non-RN group sustained significantly lower MoCA scores than the control group (28.1 ± 2.0 vs 29.1 ± 0.8, respectively; $P=.018$). A separate investigation of the effect of RN on each domain of the MoCA score demonstrated that patients in the RN group had lower scores in every domain except for orientation than the non-RN group.

Association between CMB and cognitive function

Using the multivariate logistic regression model to adjust for age, sex, education, period after radiation therapy, and brain necrosis volume, our data demonstrated that the number of CMBs in the temporal lobe was an independent risk factor for cognitive dysfunction (OR = 1.03; 95% CI: 1.01-1.04; $P=.003$). In addition, older age was also significantly associated with higher risk of cognitive dysfunction (OR = 1.07; 95% CI: 1.00-1.14; $P=.041$). A detailed summary of results of univariate and multivariate analyses is shown in Table 3. We further evaluated potential predictive value of CMBs for each cognitive domain, and the results showed that the number of CMBs in the temporal lobe was significantly associated with lower MoCA scores in visuospatial and executive abilities, language, abstraction, and delayed recall memory. In contrast, the number of CMBs in other lobes were only associated with delayed recall memory (Table 4), although, in the non-RN group, the association between temporal lobe CMBs and cognitive impairment did not exist (univariate logistic regression, $P=.113$).

Table 2 Multivariate linear regression analysis of factors associated with radiation-induced brain necrosis

Parameters	Correlation coefficient (95% CI)	*P* value
Age	1.17 (0.10-2.26)	.033*
Sex (females vs males)	−15.20 (−34.05 to 3.66)	.133
Years after radiation therapy	−0.76 (−3.09 to 1.58)	.522
Education		
Primary school	Reference	
High school	7.85 (−20.94 to 36.64)	.590
College or above	12.96 (−17.19 to 43.12)	.396
CMBs in temporal lobes	0.45 (0.26 to 0.64)	<.001*
CMBs in other lobes	0.14 (−3.47 to 3.76)	.937

Abbreviations: CMBs = cerebral microbleeds.
* Significant variables ($P<.050$).

Discussion

Our study showed that CMB is a common manifestation in patients with RN and is independently associated with an increased likelihood of cognitive dysfunction. The relationship between CMBs and cognitive dysfunction has not been described previously in RN patients but was widely investigated and reported in Alzheimer disease (AD), ischemic stroke, transient ischemic attack, vascular dementia, and cerebral small vessel disease (15-18). The underlying mechanism for increased risk of CMBs in RN has not been clarified. Our previous study reported a high prevalence of large vessel damage in RN (19). Furthermore, the production of vascular endothelial growth factor (VEGF) stimulated by radiation-induced local hypoxia has been shown to increase the permeability of the blood-brain barrier (20). Taken together, these results implied a

Table 3 Univariate and multivariate logistic regression analysis on factors associated with cognitive dysfunction

Parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.01 (0.98-1.05)	.354	1.07 (1.00-1.14)	.041*
Sex				
Male	Reference		Reference	
Females	0.49 (0.23-1.04)	.063	0.98 (0.34-2.81)	.976
Period after RT	1.07 (0.96-1.19)	.208	1.07 (0.94-1.22)	.319
Education				
Primary school	Reference		Reference	
High school	0.35 (0.11-1.07)	.066	0.31 (0.06-1.59)	.160
College or above	0.39 (0.12-1.23)	.108	0.65 (0.13-3.40)	.613
Temporal CMBs	1.04 (1.02-1.06)	<.001*	1.03 (1.01-1.04)	.003*
CMB in other lobes	1.12 (0.96-1.30)	.166	0.81 (0.62-1.06)	.120
Volume of RN (cm^3)	1.03 (1.01-1.04)	<.001*	1.01 (1.00-1.02)	.154

Abbreviations: CMBs = cerebral microbleeds; RN = radiation-induced brain necrosis; RT = radiation therapy.
* Significant variables ($P<.050$).

vessel-related pathogenesis in RN that potentially leads to increased risk of CMBs in these patients and eventually resulted in impaired cognitive function.

Increasing evidence suggests that the anatomic distribution of CMBs varies by cause. Our data demonstrated a predominance of CMBs in temporal location, which differs from the distribution of CMB locations in demented patients with other causes (15, 21-23). Previous reports have shown that lobar CMBs were related to cognitive impairment in cerebral amyloid angiopathy (16, 24). The Sunnybrook dementia study reported occipital predominance of CMBs in AD (15). On the other hand, deep CMBs in the basal ganglia were closely attributed to hypertensive microangiopathy (23). The higher occurrence of CMBs in the temporal lobe in our study cohort may be related to increased susceptibility of temporal lobes injuries induced by vicinity of radiation for NPC. In these patients, although the maximum doses delivered to the brainstem and spinal cord were generally well maintained by IMRT, the maximum doses deposited in the temporal lobes may have a higher propensity for exceeding conventional limits (25). This explanation is further endorsed by previous report of the association between the T stage of NPC and temporal lobe injury in IMRT patients, where a larger tumor extension indicated a compromise in planning dose for the temporal lobe. The reported incidence rate is between 4.8% to 16%, and may gradually increase over time after IMRT (4, 26, 27).

Our previous study also found that cognitive function was negatively correlated with the volume of RN. In the current study, after we adjusted for possible confounding factors including brain necrosis volume, age, and education, the number of CMBs still stood out as a significant predictor of cognitive dysfunction. Of note, despite demonstrating a significant influence on cognitive function in the univariate analysis, the volume of RN was not found to be significant in multivariate analysis. Our results demonstrated that CMBs have a higher predictive value of cognitive decline in RN patients than in RN volume. We also demonstrated that temporal CMBs numbers was predictive of certain domains in MoCA score but not others. The inequitable effect of temporal CMBs on each domain highlights the fact that various cognitive functions are mediated by different brain regions. Further studies are warranted to focus on the different cognitive impairments associated with various CMBs to fully appreciate the effect of CMBs on cognitive impairment in RN patients.

Our study has several limitations that need to be addressed for accurate interpretation of our results. First, the study used a cross-sectional design, which may be inadequate to describe the natural history and progression of CMBs in this population. Although an independent association was found between CMBs and cognitive dysfunction, a causal relationship of CMB as the underlying mechanism of cognitive function in RN cannot be established. Next, the patients in the control group harbored diagnosed neurological pathologies, which might indirectly have affected the assessment of cognitive function. We attempted to address this by prudently selecting our exclusion criteria and including only patients with clinical courses that were known to be unrelated to changes in cognitive function. In addition, some confounding factors such as the APOE gene, smoking, and lipid level have not been evaluated in our study. In particular, we were unable to retrieve the detail treatment planning information for all our recruited patients and, thereby, were unable to generate dosimetric variables in our study. We also included RN as an indirect indicator of organ of interest dosimetry to compensate for the information. The differences of sample size in each group also increased the risk of mismatch of the risk factors for cognitive dysfunction. A rigorous attempt to balance the baseline characteristics was established; despite a difference in sex distribution between outcome groups, we successfully proved that the independent effect of CMBs on cognitive function by analyzing the association of CMB and cognitive function in each stratum of sex.

Table 4 Multivariate logistic regression on association of risk factors and each domain within Montreal Cognitive Assessment evaluation

Domains and parameters	Correlation coefficient (95% CI)	*P* value
Visuospatial and executive abilities		
Age	−0.01 (−0.03 to 0.01)	.220
Sex (females vs males)	0.03 (−0.33 to 0.41)	.832
Years after radiation therapy	0.01 (−0.03 to 0.06)	.579
Education		
Primary school	Reference	
High school	0.17 (−0.40 to 0.73)	.561
College or above	0.11 (−0.48 to 0.70)	.704
CMBs in temporal lobes	−0.01 (−0.01 to −0.00)	.001*
CMBs in other lobes	0.07 (−0.00 to 0.14)	.057
Necrosis volume (cm^3)	−0.00 (−0.01 to 0.00)	.156
Naming		
Age	−0.01 (−0.02 to 0.01)	.335
Sex (females vs males)	0.01 (−0.19 to 0.21)	.906
Years after radiation therapy	0.00 (−0.02 to 0.03)	.887
Education		
Primary school	Reference	
High school	−0.05 (−0.35 to 0.24)	.716
College or above	−0.06 (−0.37 to 0.26)	.726
CMBs in temporal lobes	−0.00 (−0.00 to 0.00)	.725
CMBs in other lobes	0.02 (−0.02 to 0.06)	.252
Necrosis volume (cm^3)	−0.00 (−0.00 to −0.00)	.035*
Attention		
Age	−0.00 (−0.02 to 0.01)	.562
Sex (females vs males)	−0.03 (−0.29 to 0.22)	.801
Years after radiation therapy	−0.05 (−0.08 to −0.01)	.005*
Education		
Primary school	Reference	
High school	0.02 (−0.37 to 0.41)	.932
College or above	−0.22 (−0.63 to 0.19)	.295
CMBs in temporal lobes	−0.00 (−0.00 to 0.00)	.382
CMBs in other lobes	0.01 (−0.04 to 0.05)	.832
Necrosis volume (cm^3)	−0.00 (−0.01 to 0.00)	.083
Language		
Age	−0.01 (−0.02 to 0.00)	.119
Sex (females vs males)	0.05 (−0.18 to 0.28)	.665
Years after radiation therapy	−0.02 (−0.05 to 0.01)	.154
Education		
Primary school	Reference	
High school	0.10 (−0.24 to 0.45)	.559
College or above	−0.02 (−0.38 to 0.34)	.920
CMBs in temporal lobes	−0.00 (−0.01 to −0.00)	.001*
CMBs in other lobes	0.03 (−0.01 to 0.07)	.155
Necrosis volume (cm^3)	−0.00 (−0.00 to 0.00)	.730
Abstraction		
Age	−0.00 (−0.02 to 0.01)	.612
Sex (females vs males)	0.09 (−0.14 to 0.31)	.449
Years after radiation therapy	−0.01 (−0.04 to 0.01)	.356
Education		
Primary school	Reference	
High school	0.01 (−0.32 to 0.35)	.939
College or above	0.05 (−0.30 to 0.41)	.766
CMBs in temporal lobes	−0.00 (−0.01 to −0.00)	<.001*
CMBs in other lobes	0.03 (−0.01 to 0.07)	.180
Necrosis volume (cm^3)	−0.00 (−0.00 to 0.00)	.393
Delayed recall memory		
Age	−0.02 (−0.05 to 0.02)	.368
Sex (females vs males)	0.10 (−0.50 to 0.69)	.743
Years after radiation therapy	−0.09 (−0.16 to −0.02)	.014*
Education		
Primary school	Reference	
High school	0.11 (−0.79 to 1.01)	.805
College or above	−0.27 (−1.21 to 0.67)	.571
CMBs in temporal lobes	−0.01 (−0.02 to −0.01)	<.001*
CMBs in other lobes	0.12 (0.01 to 0.23)	.034*
Necrosis volume (cm^3)	−0.01 (−0.01 to 0.00)	.057
Orientation		
Age	−0.00 (−0.01 to 0.01)	.552
Sex (females vs males)	0.08 (−0.05 to 0.21)	.221
Years after radiation therapy	−0.01 (−0.02 to 0.01)	.400
Education		
Primary school	Reference	
High school	−0.04 (−0.23 to 0.16)	.692
College or above	−0.19 (−0.40 to 0.01)	.062
CMBs in temporal lobes	−0.00 (−0.00 to 0.00)	.663
CMBs in other lobes	−0.01 (−0.04 to 0.01)	.339
Necrosis volume (cm^3)	−0.00 (−0.00 to 0.00)	.639

* Significant variables ($P<.050$).

Despite these limitations, we demonstrated that CMBs were independently associated with RN and post-treatment cognitive dysfunction. With a cross-sectional design, we cannot provide the temporal profile of the development of

CMBs, thereby rendering our results insufficient to establish a causal relationship between CMBs and RN. However, the clinical implications of our current findings cannot be ignored. First, our results indirectly endorse the theory that microvascular injury may be involved in the development of RN. Therefore, interventions or medications targeted at repairing microvascular injury are potentially effective in prevention of RN, although further studies are warranted to fully explore that possibility. Next, provided with the fact that the number of CMBs can be easily assessed without additional radiological exams except for follow-up MRIs, it might pose as an optimal indicator of cognitive function prognosis, and become useful in predicting RN development. Personalized and accurate prediction of functional outcomes helps physicians to provide better education and preparation for patients and their families to cope with anticipated decline of post-treatment cognitive function. Finally, with the exploratory aim of this study, we hope to see more future studies investigating the underlying causal relationships among CMBs, RN, and cognitive function, with a particular focus on longitudinal assessment of post-radiation CMBs.

Conclusions

In conclusion, this study demonstrates that the number of CMBs following radiation therapy is associated with decline of cognitive function. This association is independent of age, education, post-radiation interval, and volume of brain necrosis. Our findings suggested the potential value of CMBs for early diagnosis and treatment of cognitive dysfunction in RN.

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